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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,073	12/07/2001	Anthony M. Jevnikar	024916-011	8806

7590 02/10/2004

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,073	JEVNIKAR ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-101* is/are pending in the application.

4a) Of the above claim(s) *53-58,62,64-68,92-94 and 96-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52,59-61,63,69-91 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group II, Claims 63-71, 78-83, and 95-96, and the species, "the transplantation antigen MHC Class II protein", filed 10/27/03, is acknowledged. Applicant is advised that, upon reconsideration, the restriction requirement is hereby withdrawn. The election of species requirement is however, maintained. Regarding said requirement, while Applicant has elected the species, MHC Class II protein, with traverse, Applicant has provided no specific argument in support of said traversal. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 53-58, 62, 64-68, 92-94, and 96-101 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to nonelected species. Note that "transplantation antigens" are not autoantigens (they are allogeneic), accordingly, all claims drawn to autoantigens are considered to be drawn to nonelected species.

Claims 52, 59-61, 63, 69-91, and 95 are being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 52, 59-61, 63, 69-91, and 95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding *in vivo* methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the biological arts were such that no methods were available in 1994 for inducing oral tolerance to a transplantation antigen in a human. Indeed, some 10 years later, with the possible exception of some allergy and Rh antigens, therapeutic tolerance has not been demonstrated to be inducible in humans.

Note that the claims comprise both product and method claims. Also note that only Claims 77 and 83 recite the limitation that the method and products are intended for use in humans. It is clear however, that the products of the claims are intended for just one use, i.e., the induction of oral tolerance to transplantation antigens. It is also well-known that transplantation is performed almost exclusively in humans. Accordingly, all of the claims under examination are rejected for lack of enablement.

Attempts to induce tolerance in humans have been completely unsuccessful in at least two different documented instances. See for example, *Marketletter* (9/13/99) which teaches the complete failure of tolerance induction in human trials. Both Myloral (for multiple sclerosis) and Colloral (for rheumatoid arthritis) provided successful results in inducing tolerance in animal models, however, both were complete failures in human trials. Also note an additional more recent reference (Goodnow, 2001), wherein the author flatly states, "Obtaining the desired response [tolerance] with these strategies [tolerance induction] is unpredictable because many of these signals [tolerogenic] have both tolerogenic and immunogenic roles," (see the Abstract). The

author goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in humans because of the lack of understanding of the mechanisms involved (page 2120, column 2). WO 02/053092 teaches that the oral administration of antigens for the induction of tolerance presents numerous additional "obstacles" including the problem of accurate dosing given the necessity of digestion which alters both concentration and structure of the antigens. In that work the inventors conclude that "oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even *in vitro* results, and must result from extensive empirical experimentation," (page 23). Clearly then, the brief teachings of the instant disclosure, wherein no *in vivo* nor even *in vitro* data is disclosed, cannot be considered to be enabling for the method and products of the instant claims.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses no data relevant to the induction of tolerance, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 52, 59-61, 63, 69-91, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/07581 (1992, IDS) in view of U.S. Patent No. 5,484,719 (IDS).

WO 92/07581 teaches a method (and product) for the induction of tolerance to MHC Class II proteins through the oral administration of an effective immunosuppressive dose of said proteins as a method for suppressing the rejection of engrafted donor tissues in humans (see particularly Summary of Invention, pages 7-8 and Class II MHC molecules pages 11-12).

The reference teaching differs from the claimed invention only in that it does not teach the use of a transgenic plant as the source of the oral tolerizing antigen.

The '719 patent teaches that transgenic plants comprise an inexpensive and convenient source of edible oral vaccines (antigens) (see particularly column 4, lines 7-21). The reference further teaches a DNA construct for transforming a plant comprising a Cauliflower Mosaic Virus 35S promoter (see particularly column 8, lines 41-45) and nopaline synthase termination sequence (see particularly column 9, lines 29-30), and that said vaccines comprise partially purified extracts of leaves, stems, and seeds (see particularly column 6, line 60) of a potato or a tomato (see particularly column 7, lines 10-15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method(and produce a product) for the induction of tolerance to MHC Class II proteins through the oral administration of an effective immunosuppressive dose of said proteins as a method for suppressing the rejection of engrafted donor tissues in humans, as taught by WO 92/07581. One of ordinary skill in the art at the time the invention was made would have been motivated to produce the antigen for said tolerance induction in the transgenic plant of the '719 patent comprising a DNA construct for transforming a plant, said construct comprising a Cauliflower Mosaic Virus 35S promoter and a nopaline synthase termination sequence, said antigen further comprising a partially purified extract of leaves, stems, and seeds of a potato or a tomato, because said transgenic plant would have provided an inexpensive and convenient source of said antigen, again as taught by the '719 patent. Note that the '719 patent teaches the administration of oral antigens for the induction of an immune response whereas the instant claims are drawn to the administration of oral antigens for the induction of tolerance. However, the induction of tolerance and the induction of an immune response can be considered two sides of the same coin. Indeed, some immunologists refer to the induction of tolerance as the induction of a suppressive immune response. Thus, the use of a transgenic plant as the source of an antigen for the induction of an immune response renders the use of a transgenic plant as the source of an antigen for the induction of tolerance obvious.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

Please Note: inquiries of a general nature or relating to the status of this application should not be directed to the Examiner but rather should be directed to the Technology Center 1600 Customer Service Center at (703) 308-0198.

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2/2/04
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